EXHIBIT 27

CONNETICS CORP

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DEFR14A

DEFINITIVE PROXY STATEMENT – REVISED
Filed on 04/21/2006
File Number 000–27406

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

SCHEDULE 14A

Proxy Statement Pursuant to Section 14(a) of the Securities Exchange Act of 1934 (Amendment No. 1)

Filed by the Registrant ☒
Filed by a Party other than the Registrant ☐
Check the appropriate box:

☐ Preliminary Proxy Statement
☐ **Confidential, for Use of the Commission Only (as permitted by Rule 14a–6(e)(2))**
☒ Definitive Proxy Statement
☐ Definitive Additional Materials
☐ Soliciting Material Pursuant to §240.14a–12

Connetics Corporation

(Name of Registrant as Specified In Its Charter)

(Name of Person(s) Filing Proxy Statement, if other than the Registrant)

Payment of Filing Fee (Check the appropriate box):

☒ No fee required.
☐ Fee computed on table below per Exchange Act Rules 14a–6(i)(1) and 0–11.

(1) Title of each class of securities to which transaction applies:

(2) Aggregate number of securities to which transaction applies:

(3) Per unit price or other underlying value of transaction computed pursuant to Exchange Act Rule 0–11 (set forth the amount on which the filing fee is calculated and state how it was determined):

(4) Proposed maximum aggregate value of transaction:

(5) Total fee paid:

☐ Fee paid previously with preliminary materials.

☐ Check box if any part of the fee is offset as provided by Exchange Act Rule 0–11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.

(1) Amount Previously Paid:

(2) Form, Schedule or Registration Statement No.:

(3) Filing Party:

(4) Date Filed:

STOCK OWNERSHIP

Who are the largest owners of Connetics stock, and how much stock do our directors and executive officers own?

The following table sets forth certain information we know with respect to the beneficial ownership of our common stock as of March 24, 2006 by (a) all persons who are beneficial owners of more than five percent of our common stock, (b) each director and nominee, (c) each of our executive officers named in the Summary Compensation Table below, and (d) all director nominees, current directors and executive officers as a group.

Beneficial ownership is determined in accordance with the rules and regulations of the SEC and generally includes voting or investment power with respect to securities. Percentage ownership is based on 34,224,303 shares of common stock outstanding at March 24, 2006, which excludes 3,357,307 treasury shares. Except as indicated otherwise in the footnotes below, and subject to community property laws where applicable, we believe that the persons named in the table below have sole voting and investment power with respect to all shares of common stock shown.

Name	Number of Shares	Percentage of Shares Outstanding	Footnote(s)
Wellington Management Company, LLP 75 State Street Boston, Massachusetts 02109	2,670,563	7.8%	(1)
Barclays Global Investors, N.A. Barclays Global Fund Advisors Barclays Bank PLC Barclays Capital Securities Limited 45 Fremont Street San Francisco, CA 94105	2,039,830	5.96%	(2)
Capital Research and Management Company and SMALLCAP World Fund, Inc. 333 South Hope Street Los Angeles, CA 90071	2,000,000	5.84%	(3)
Thomas G. Wiggans	1,526,247	4.30%	(4)
C. Gregory Vontz	737,707	2.12%	(5)
John L. Higgins	603,625	1.74%	(6)
G. Kirk Raab	492,790	1.42%	(7)
Katrina J. Church	400,054	1.16%	(8)
Thomas D. Kiley	258,615	*	(9)
Lincoln Krochmal, M.D.	214,193	*	(10)
John C. Kane	149,939	*	(11)
Denise M. Gilbert, Ph.D.	61,111	*	(12)
Leon E. Panetta	53,264	*	(13)
R. Andrew Eckert	53,611	*	(14)
Carl B. Feldbaum	30,000	*	(15)
David E. Cohen, M.D.	0	*	
All directors and officers as a group (26 persons)	5,372,569	13.91%	(16)

* Less than 1%.

(1) As reported on a Schedule 13G/ A filed with the SEC on or about December 30, 2005. Represents 2,670,563 shares as to which Wellington Management Company, LLP has shared dispositive power, and 2,538,863 shares as to which Wellington Management Company, LLP has shared voting power, with the unnamed beneficial owners, who are clients of Wellington Management Company, LLP.

(2) As reported on a Schedule 13G/ A filed with the SEC on or about December 31, 2004 by Barclays Global Investor, N.A. and a group of affiliated entities. According to the Schedule 13G/ A, the following entities have sole voting power with respect to an aggregate of 1,885,547 shares and dispositive power with respect to an aggregate of 2,039,830 shares held in trust accounts for the economic benefit of the beneficiaries of those accounts: Barclays Global Investors, N.A., (828,606 shares, voting power and 982,889 shares, dispositive power); Barclays Global Fund Advisors (707,844 shares); Barclays Bank PLC (338,611 shares); and Barclays Capital Securities Limited (10,486 shares).

(3) As reported on a Schedule 13G filed with the SEC on or about December 30, 2005. Represents 2,000,000 shares as to which Capital Research and Management Company, an investment adviser registered under Section 203 of the Investment Advisers Act of 1940 has sole dispositive and voting power. Capital Research and Management Company is deemed to be the beneficial owner of and as a result is acting as investment advisor to various investment companies registered under Section 8 of the Investment Company Act of 1940. SMALLCAP World Fund, Inc., an investment company registered under the Investment Company Act of 1940, which is advised by Capital Research and Management Company, is the beneficial owner of 2,000,000 shares.

(4) Mr. Wiggans' total includes options to purchase 1,244,275 shares of common stock that will be exercisable on or before May 23, 2006. Also includes 10,490 shares held by Mr. Wiggans' wife, and 12,486 shares held in trust for Mr. Wiggans' children. Mr. Wiggans disclaims beneficial ownership of the shares held in trust.

(5) Mr. Vontz's total includes options to purchase 608,887 shares of common stock that will be exercisable on or before May 23, 2006.

(6) Mr. Higgins' total includes options to purchase 468,256 shares of common stock that will be exercisable on or before May 23, 2006. Also includes 250 shares of common stock held by Mr. Higgins' wife.

(7) Mr. Raab's total includes options to purchase 474,950 shares of common stock that will be exercisable on or before May 23, 2006.

(8) Ms. Church's total includes options to purchase 346,218 shares of common stock that will be exercisable on or before May 23, 2006.

(9) Mr. Kiley's total includes options to purchase 77,500 shares of common stock that will be exercisable on or before May 23, 2006. Also includes 167,365 shares held in the Thomas D. and Nancy L.M. Kiley Revocable Trust under Agreement dated August 7, 1981, and 10,000 shares held in The Kiley Family Partnership of which Mr. Kiley is a trustee, and as to 7,500 of which Mr. Kiley disclaims beneficial ownership.

(10) Dr. Krochmal's total includes options to purchase 153,333 shares of common stock that will be exercisable on or before May 23, 2006.

(11) Mr. Kane's total includes options to purchase 122,500 shares of common stock that will be exercisable on or before May 23, 2006.

(12) Dr. Gilbert's total includes options to purchase 60,000 shares of common stock that will be exercisable on or before May 23, 2006.

(13) Mr. Panetta's total includes options to purchase 45,000 shares of common stock that will be exercisable on or before May 23, 2006.

(14) Mr. Eckert's total includes options to purchase 52,500 shares of common stock that will be exercisable on or before May 23, 2006.

(15) Mr. Feldbaum's total includes options to purchase 30,000 shares of common stock that will be exercisable on or before May 23, 2006.

(16) See footnotes 4 through 15. The total includes options to purchase an aggregate of 4,395,829 shares of common stock that will be exercisable on or before May 23, 2006 by all of the officers and directors as a group.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Exchange Act requires our directors and certain executive officers, and any person who beneficially owns more than 10% of our common stock, to file reports of their holdings and transactions in Connetics stock with the SEC. Based on our records and other information, including a review of the copies of those reports furnished to us and written representations that no other reports were required to be filed, we believe that all of our directors and executive officers complied during 2005 with the filing requirements under Section 16(a), with one exception, which resulted from an administrative error on the part of the Company. As a result, the following outside directors who automatically received stock options on April 22, 2005 when they were re–elected to the Board, did not file reports with the SEC until May 17, 2005: Dr. Barkas, Dr. Bauer, Mr. Eckert, Dr. Gilbert, Mr. Kane, Mr. Kiley, Mr. Panetta, and Mr. Raab. Based solely on a review of copies of reports furnished to us, we believe that the beneficial owners of more than 10% of our common stock timely complied with all filing requirements under Section 16(a) for the year ended December 31, 2005.

CORPORATE GOVERNANCE

Our Commitment to Good Corporate Governance

We believe that good corporate governance and an environment of the highest ethical standards are important for Connetics to achieve business success and to create value for our stockholders. We continuously review our corporate governance practices in view of the Sarbanes–Oxley Act of 2002, rules of the SEC and Nasdaq listing rules. We also compare and conform as needed our governance practices with those identified as best practices by various authorities and other public companies. As a result, we continue to evaluate and strengthen the corporate governance processes at Connetics.

Management Executive Committee

The management Executive Committee has responsibility for the overall direction, strategy and operations of Connetics, including, among other things, corporate financial performance, commercial performance, research, development and product operations performance, and employee development performance. The six members of the management Executive Committee hold the following positions at Connetics:

- Chief Executive Officer,
- President and Chief Operating Officer,
- Executive Vice President, Finance and Corporate Development, and Chief Financial Officer,
- Executive Vice President, General Counsel and Secretary,
- Executive Vice President, Research and Product Development, and
- Senior Vice President, Technical Operations.

Board Meetings and Committees

While Connetics' executives are responsible for our daily operations, the Board manages our corporate resources, and is responsible for establishing broad corporate policies and for overseeing the overall performance of Connetics and management. The Board reviews significant developments affecting Connetics and acts on matters requiring Board approval, and reviews our corporate governance policies and practices. This review includes comparison of our current policies and practices to those mandated by legislation and regulation, including the Sarbanes–Oxley Act of 2002, regulations proposed or adopted by the SEC, and Nasdaq listing standards. This review also includes an assessment of policies and practices

EXHIBIT 28

OFFICE OF NEW DRUGS

NDAs: Filing Review Issues

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PURPOSE

- This MAPP establishes procedures for identifying review issues during the filing review of all original NDA applications and efficacy supplements within the Center for Drug Evaluation and Research (CDER) and outlines the procedures for informing the applicant about these issues. It does not apply to labeling supplements that contain clinical data.

BACKGROUND

- On June 12, 2002, the President signed the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, which includes the Prescription Drug User Fee Amendments of 2002 (PDUFA III). In conjunction with the June 2002 reauthorization of PDUFA, FDA agreed to meet specific performance goals (PDUFA Goals). The PDUFA Goals outline the basic requirements for first cycle review performance, including applicant notification of issues identified during the filing review.

- The June 2002 reauthorization of PDUFA performance goals directed FDA to "report substantive deficiencies identified in the initial filing review to the sponsor by letter, telephone conference, facsimile, secure e-mail, or other expedient means."

REFERENCES

- *PDUFA Reauthorization Performance Goals and Procedures*, an enclosure to a letter dated June 4, 2002, from the Secretary of Health and Human Services, Tommy Thompson, to Congress, available at http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html

- FDA/CDER guidance for industry on *Refusal to File*

DEFINITION

- **Filing review issues:** Substantive deficiencies or concerns identified by the review team during the initial filing review for an NDA or efficacy supplement that appear to have been inadequately addressed in the application and merit particular attention during the review process. These issues may have significant impact on the Agency's ability to complete the review of the application or approve the application or parts of the application. Filing review issues are distinct from application deficiencies that serve as the basis for a Refusal to File action. Filing review issues pertain only to applications that have been filed.

POLICY

- Any filing review issues identified during the filing review will be communicated to the applicant no later than 14 calendar days after the 60-day filing date.

- If the review team does not identify any filing review issues, the applicant will be informed of this fact no later than 14 calendar days after the 60-day filing date.

- This MAPP applies only to original NDA applications and original efficacy supplements. It does not apply to labeling supplements that contain clinical data.

PROCEDURES

- **Identification of Filing Review Issues:** During the initial filing review of a newly submitted original NDA or efficacy supplement, any issues that may meet the definition of a filing review issue should be identified and discussed within the review team (e.g., at a 45-day filing meeting). The review team can request a response from the applicant on any number or none of the identified issues.

- **Communication of Filing Review Issues to Applicant:** All filing review issues identified by the review team will be conveyed to the applicant in a single communication, which will include the Agency's expectations for applicant responses, if any. This communication may be by letter, telephone conference, facsimile, secure e-mail, or other expedient means, and should be made within the specified time frame.

- **Documentation of Filing Review Issues:** Communication of filing review issues to the applicant will be documented in writing and archived using standard CDER processes.

RESPONSIBILITIES

Review Team Members will:

- Identify any potential filing review issues during the filing review and inform the other members of the review team about these issues at or before the filing meeting.

- For each filing review issue, determine whether to request a response from the applicant.

Team Leaders,
Chiefs, Project Management Staff,
and Review Division Directors will:

- Provide guidance to the review team about identifying potential filing review issues and distinguishing any internal review discussion points that do not meet the definition of filing review issues.

- Determine the appropriateness of the filing review issues to be conveyed to the applicant.

Review Division Project Management Staff will:

- Convey and/or confirm conveyance of filing review issues, or lack thereof, to the applicant within the designated time frame, including standard language on the preliminary nature of these findings.

- Document in writing conveyance of filing review issues, or lack thereof, to applicant.

AUTHORITY

- Following discussion with the entire review team, if filing review issues are identified for multiple review disciplines, the Chief, Project Management Staff, or Review Division Director should authorize communication of that information to the applicant. If all filing review issues pertain to only one review discipline, the relevant review discipline team leader can authorize this communication.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

EXHIBIT 29

PHARMACOLOGY AND TOXICOLOGY

DISTRIBUTION OF FINAL REPORTS FROM THE CARCINOGENICITY ASSESSMENT COMMITTEE (CAC) AND EXECUTIVE CAC

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PURPOSE This MAPP establishes the policies and procedures by which the review divisions will provide sponsors with the final reports from the Carcinogenicity Assessment Committee (CAC) and the Executive CAC.

BACKGROUND

The CAC conducts a tertiary review of carcinogenicity studies in accordance with MAPP 7412.1, *Management of CDER Carcinogenicity Assessment Committee (CAC) and Executive CAC*. The CAC review is of interest to sponsors who often request it from the review divisions.

The review divisions are responsible for all direct communication with sponsors, including recommendations from the CAC and Executive CAC. Since carcinogenicity studies submitted to the Center for Drug Evaluation and Research (CDER) should be reviewed by the CAC or Executive CAC, it is important that a mechanism to consistently communicate the CAC recommendations to sponsors is established. To achieve this objective, this guide describes the policy and procedures for releasing CAC final reports.

REFERENCES

- CDER MAPP 7412.1, *Management of CDER Carcinogenicity Assessment Committee (CAC) and Executive Committee*.

POLICY

- This policy applies to all final reports documenting the deliberations and recommendations of the CAC and the Executive CAC. Final reports should be provided to sponsors by the reviewing division upon written request by the sponsor.

- The recommendations in a CAC and Executive CAC final report of the carcinogenicity study results are advisory to the review divisions and office directors. These reports aid in the interpretation of the carcinogenicity study results and the potential relevance of the findings under the conditions of clinical use.

- The final reports generated by the CAC or Executive CAC on the dose selection and study design for proposed carcinogenicity protocols provide Center concurrence and/or recommendations for sponsors and are to be conveyed to the sponsor.

PROCEDURES

Releasing CAC and Executive CAC final reports:

- The review division should inform the sponsor when a proposed carcinogenicity protocol or study results will be reviewed by the CAC or Executive CAC. The final report for the protocol evaluation will be made available 75 days from the CDER receipt stamp date of the protocol.

- Upon written request, the full reports the CAC evaluation of the carcinogenicity study will be made available 30 days after the CAC meeting.

- The final report should be provided with a cover letter from the Division Director (or designate) clearly stating that the recommendations made by the CAC on carcinogenicity study evaluations are advisory and should not be interpreted by the sponsor as a measure of the approvability of their application.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

EXHIBIT 30

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-756

FINAL PRINTED LABELING

BenzaClin™ Topical Gel

Rx Only

(clindamycin - benzoyl peroxide gel)

Topical Gel: clindamycin (1%) as clindamycin phosphate, benzoyl peroxide (5%)
For Dermatological Use Only - Not for Ophthalmic Use
Reconstitute Before Dispensing

DESCRIPTION

BenzaClin™ Topical Gel contains clindamycin phosphate, (7(S)-chloro-7-deoxylincomycin-2-phosphate). Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

Chemically, clindamycin phosphate is ($C_{18}H_{34}ClN_2O_8PS$). The structural formula for clindamycin is represented below:

Insert
Clindamycin stucture
(see USP Dictionary of USAN and International Drug Names 1997 p. 173)

Clindamycin phosphate has molecular weight of 504.97 and its chemical name is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans- 4-propyl-L-2-pyrrolidinecarboxamido) - 1-thio-L- threo-alpha-D- galacto-octopyranoside 2-(dihydrogen phosphate).

BenzaClin Topical Gel also contains benzoyl peroxide, for topical use.
Chemically, benzoyl peroxide is ($C_{14}H_{10}O_4$). It has the following structural formula:

Insert
Benzoyl Peroxide stucture
(see USP Dictionary of USAN and International Drug Names 1997 p. 87)

Benzoyl peroxide has a molecular weight of 242.23.

Each gram of **BenzaClin Topical Gel** contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, sodium hydroxide, dioctyl sodium sulfosuccinate, and purified water.

CLINICAL PHARMACOLOGY

An *in vitro* percutaneous penetration study comparing **BenzaClin Topical Gel** and topical 1% clindamycin gel alone, demonstrated there was no statistical difference in penetration between the two drugs. Mean systemic bioavailability of topical clindamycin in **BenzaClin Topical Gel** is suggested to be less than 1%.

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. Less than 2% of the dose enters systemic circulation as benzoic acid. It is suggested that the lipophilic nature of benzoyl peroxide acts to concentrate the compound into the lipid-rich sebaceous follicle.

Microbiology:

The clindamycin and benzoyl peroxide components individually have been shown to have in vitro activity against *Propionibacterium acnes* an organism which has been associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in clinical trials with this product.

CLINICAL STUDIES

In two adequate and well controlled clinical studies of 758 patients, 214 used BenzaClin, 210 used benzoyl peroxide, 168 used clindamycin, and 166 used vehicle. BenzaClin applied twice daily for 10 weeks was significantly more effective than vehicle in the treatment of moderate to moderately severe facial acne vulgaris. Patients were evaluated and acne lesions counted at each clinical visit; weeks 2, 4, 6, 8 and 10. The primary efficacy measures were the lesion counts and the investigator's global assessment evaluated at week 10. Patients were instructed to wash the face with a mild soap, using only the hands. Fifteen minutes after the face was thoroughly dry, application was made to the entire face. Non-medicated make-up could be applied at one hour after the BenzaClin application. If a moisturizer was required, the patients were provided a moisturizer to be used as needed. Patients were instructed to avoid sun exposure. Percent reductions in lesion counts after treatment for 10 weeks in these two studies are shown below:

Study 1			
BenzaClin n=120	Benzoyl peroxide n=120	Clindamycin n=120	Vehicle n=120
Mean percent reduction in inflammatory lesion counts			
46%	32%	16%	+ 3%
Mean percent reduction in non-inflammatory lesion counts			
22%	22%	9%	+1%
Mean percent reduction in total lesion counts			
36%	28%	15%	0.2%

Study 2			
BenzaClin n=95	Benzoyl peroxide n=95	Clindamycin n=49	Vehicle n=48

Mean percent reduction in inflammatory lesion counts			
63%	53%	45%	42%
Mean percent reduction in non-inflammatory lesion counts			
54%	50%	39%	36%
Mean percent reduction in total lesion counts			
58%	52%	42%	39%

The BenzaClin group showed greater overall improvement than the benzoyl peroxide, clindamycin and vehicle groups as rated by the investigator.

INDICATIONS AND USAGE

BenzaClin Topical Gel is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS

BenzaClin Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

WARNINGS

ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBIOTIC FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY CLOSTRIDIA IS ONE PRIMARY CAUSE OF ANTIBIOTIC- ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERSISTENT DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR *Clostridium Difficile* AND STOOL ASSAY FOR *Clostridium Difficile* TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIPERISTALTIC AGENTS SUCH AS OPIATES AND DIPHENOXYLATE WITH ATROPINE MAY PROLONG AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS, AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSATION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vitro antagonism is not known.

Information for Patients: Patients using **BenzaClin Topical Gel** should receive the following information and instructions:

1. **BenzaClin Topical Gel** is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.

2. This medication should not be used for any disorder other than that for which it was prescribed.

3. Patients should not use any other topical acne preparation unless otherwise directed by physician.

4. Patients should report any signs of local adverse reactions to their physician.

5. **BenzaClin Topical Gel** may bleach hair or colored fabric.

6. Store refrigerated 2 to 8°C (36 to 46°F). Do not freeze. Discard any unused product after 2 months.

7. Before applying **BenzaClin Topical Gel** to affected areas wash the skin gently, then rinse with warm water and pat dry.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced skin tumors in transgenic Tg.AC mice in a study using 20 weeks of topical treatment.

Genotoxicity studies were not conducted with BenzaClin Topical Gel. Clindamycin phosphate was not genotoxic in Salmonella typhimurium or in a rat micronucleus test. Clindamycin phosphate sulfoxide, an oxidative degradation product of clindamycin phosphate and benzoyl peroxide, was not clastogenic in a mouse micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in Salmonella typhimurium tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with **BenzaClin Topical Gel** or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g BenzaClin Topical Gel, based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C:
Animal reproductive/developmental toxicity studies have not been conducted with BenzaClin Topical Gel or benzoyl peroxide. Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

There are no well-controlled trials in pregnant women treated with **BenzaClin Topical Gel**. It also is not known whether **BenzaClin Topical Gel** can cause fetal harm when administered to a pregnant woman.

Nursing Women: It is not known whether **BenzaClin Topical Gel** is excreted in human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be make whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS

During clinical trials, the most frequently reported adverse event in the BenzaClin treatment group was dry skin (12%). The Table below lists local adverse events reported by at least 1% of patients in the BenzaClin and vehicle groups.

Local Adverse Events - all causalities in >/= 1% of patients		
	BenzaClin n = 420	Vehicle n = 168
Application site reaction	13 (3%)	1 (<1%)
Dry skin	50 (12%)	10 (6%)
Pruritus	8 (2%)	1 (<1%)
Peeling	9 (2%)	-
Erythema	6 (1%)	1 (<1%)
Sunburn	5 (1%)	-

The actual incidence of dry skin might have been greater were it not for the use of a moisturizer in these studies.

DOSAGE AND ADMINISTRATION

BenzaClin Topical Gel should be applied twice daily, morning and evening, or as directed by a physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry.

HOW SUPPLIED AND COMPOUNDING INSTRUCTIONS

Size (Net Weight)	**NDC 0066-**	**Benzoyl Peroxide Gel**	**Active Clindamycin Powder (In plastic vial)**	**Purified Water To Be Added**
25 grams	0494-25	19.7g	0.3g	5 mL

Prior to dispensing, tap vial until powder flows freely. Add purified water to vial (to the mark) and immediately shake to completely dissolve clindamycin. If needed, add additional purified water to bring level up to the mark. Add this solution to gel and stir until homogenous in appearance (1 to 1½ minutes). **BenzaClin Topical Gel** should then be stored under refrigeration. Do not freeze. Place a 2-month expiration date on the label immediately following mixing. Place a STORE REFRIGERATED sticker onto the jar.

NOTE:

Prior to reconstitution, store at Controlled Room Temperature 20 to 25°C (68 to 77°F)[see USP].

After reconstitution, store refrigerated 2 to 8°C (36 to 46°F).

Do not freeze. Keep tightly closed. Keep out of the reach of children.
US Patents 5,446,028; 5,767,098; 6,013,637IN-xxxx Rev. mm/yy

DERMIK LABORATORIES, INC.
Berwyn, PA 19312 USA

APPEARS THIS WAY
ON ORIGINAL

/s/

Jonathan Wilkin
12/21/00 12:51:18 PM

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT 31

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-756

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-756

Dermik Laboratories, Inc.
Attention: Kim Forbes-McKean, Ph.D.
Senior Director, Product Development and Commercialization
1050 Westlakes Drive
Berwyn, PA 19312

Dear Dr. Forbes-McKean:

Please refer to your new drug application (NDA) dated April 9, 1998, received April 10, 1998, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for BenzaClin (clindamycin 1% and benzoyl peroxide 5% gel) Topical Gel.

Please refer to our action letter dated April 1, 1999.

We acknowledge receipt of your submissions dated June 29, July 7, August 4, September 20, and October 17, 2000. Your submission of June 29, 2000, received June 30, 2000, constituted a complete response to our April 1, 1999, action letter.

This new drug application provides for the use of BenzaClin (clindamycin 1% and benzoyl peroxide 5% gel) Topical Gel for the treatment of acne vulgaris.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 50-756." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your post marketing commitments specified in your facsimile dated December 20, 2000. You have agreed to submit the following protocols within 9 months of the approval of this application:

1. To conduct a dermal carcinogenicity study and a study on the effects on UV-induced skin carcinogenicity. These studies should be completed and submitted within 4 years of the approval of this application.

2. To conduct a study in patients with acne vulgaris designed to assess the degree of systemic absorption of clindamycin under maximal use conditions (i.e. maximizing the amount applied, surface area involved, and frequency of application consistent with the approved package insert). Such a study should be done under multiple dosing conditions and include a representative range of ages of both sexes. This *in vivo* pharmacokinetic study should be completed and submitted within 18 months of approval of this application.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your post marketing commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these post marketing commitments must be clearly designated "Post Marketing Commitments."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving pediatric studies below the age of 12 years, because acne is not prevalent in the population from birth to 11 years, and this product would not represent a substantive therapeutic benefit as an acne therapy for that population. There are sufficient data to determine efficacy and safety down to and including age 12 years. The Agency grants you a partial waiver for pediatric acne studies for the age group between birth and 11 years of age, under 21 CFR 314.55(c)(4)

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Kevin Darryl White, Project Manager, at (301) 827-2020.

Sincerely,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 50-756
HFD-540/Div. Files
HFD-540/White (with labeling) 11.17.00
HFD-540/Kozma-Fornaro (with labeling) 11.17.00
HFD-540/Wilkin (with labeling)
HFD-540/Walker (with labeling) 11.17.00
HFD-540/Huene (with labeling)
HFD-540/DeCamp (with labeling) 11.21.00
HFD-540Vidra (with labeling) 11.21.00
HFD-540/Jacobs (with labeling) 11.17.00
HFD-540Mainigi (with labeling)
HFD-540/Bashaw (with labeling) 11.21.00
HFD-540/Al-Osh (with labeling)
HFD-540/Thomson (with labeling)
HFD-520/A. Sheldon/Marsik (with labeling)
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-105/ADRA (with labeling)
HFD-104/Peds/V.Kao (with labeling)
HFD-104/Peds/T.Crescenzi (with labeling)
HFD-42/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-093/DDMS-IST (with labeling)
HFD-830/DNDC Division Director (with labeling)
DISTRICT OFFICE

Drafted by: KDW 11-17-00 02:45pm
Initialed by:
Final:
Filename: NDA 50-756 BenzaClin AP 11-20-00

APPROVAL (AP)

EXHIBIT 32

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-535

ADMINISTRATIVE DOCUMENTS

Division Director's Summary Review of NDA 21-535

Sponsor:	Galderma Laboratories, L.P. 14501 North Freeway Forth Worth, TX 76177 USA
Generic name:	Clobetasol Propionate
Trade name:	Clobex
Chemical name:	Clobetasol Propionate
Pharmacologic Category:	Anti-inflammatory
Indication:	Moderate to Severe Plaque Psoriasis and — Dermatitis
Dosage Forms (s):	Lotion
Route (s) of Administration:	Topical

I. Reviewing Disciplines' Conclusions:

A. Chemistry Review dated 6/27/03:

"After evaluation for GMP compliance, all three manufacturing and testing facilities were found to be acceptable. Clobetasol propionate, is a well-established chemical whose structure has been fully elucidated. It is characterized through the USP monograph, and listed in USAN and in the Merck Index (additional data). The DMF of the main drug substance supplier has been updated, reviewed and found to be adequate. The NDA submission and its amendments (responses to information request letters) provide adequate information on the chemistry, manufacturing and controls for the production of Clobex (clobetasol propionate) Lotion, 0.05%.

"From a chemistry, manufacturing and controls standpoint (sic: it) is approvable pending action by the applicant to withdraw [redacted] as an alternate [redacted] supplier."

The applicant withdrew the reference to DMF [redacted] pertaining to [redacted] in correspondence dated July 1, 2003, resolving the sole remaining CMC approvability issue.

B. Pharmacology/Toxicology Review dated 3/20/03:

"The nonclinical studies conducted by the sponsor confirm that clobetasol propionate has teratogenic potential. A teratogencity study in rats using the dermal route resulted in dose related maternal toxicity and fetal effects from 0.05 to 0.5 mg/kg/day of Clobetasol propionate. These doses are approximately 0.14 to 1.4 times, respectively, the human topical dose of Clobetasol Propionate Lotion, 0.05%. Abnormalities seen included low fetal weights, umbilical herniation, cleft palate, reduced skeletal ossification other skeletal abnormalities. Other nonclinical findings suggest that the lotion did not cause skin sensitization and was not irritating to the skin or eye."

No new pharmacology information was submitted by the sponsor, since this was a 505(b)(2).

"No new safety issues relevant to clinical use have been identified in the studies conducted by the sponsor. The teratogenic potential of clobetasol propionate is addressed in the label.

"The application is approvable from a pharm/tox perspective provided the sponsor agrees to conduct the recommended phase 4 nonclinical studies.

"It is recommended that the sponsor be asked to agree to conduct a dermal carcinogenicity study and an evaluation of the photocarcinogenic potential of the drug product as phase 4 commitments."

C. Clinical Pharmacology & Biopharmaceutics Review dated 7/1/03:

"From a Biopharmaceutics perspective the firm has provided evidence of systemic availability for the test Clobex Propionate Lotion and reference Temovate E Emollient cream formulations. Based on the results of the 3 HPA axis trials, use of CP Lotion is clearly associated with a high incidence of HPA suppression compared to the Temovate E Emollient cream. Thus, from a clinical pharmacology perspective, there is a reasonable concern about the safety of this product in uncontrolled administration. While the bioavailability of clobetasol has been determined via indirect methods (i.e., HPA axis testing), the safety issues raised by the increased bioavailability relative to the reference product raises a significant concern."

The basis for the "significant concern" is that this product is "clearly associated with a high incidence of HPA suppression compared to the Temovate E Emollient Cream." This "significant concern" of "the safety issues raised by the increased bioavailability" will be addressed in the discussion of the Clinical Review (below).

D. Biostatistics Review dated 5/7/03:

The ITT analysis with LOCF for missing data demonstrated that Clobex Lotion is superior to its vehicle for all primary endpoints in Studies 9707 (psoriasis), 18001 (atopic dermatitis), and 2651 (psoriasis). Study 2651 was regarded as supportive and Studies 9707, and 18001 as pivotal, by both the Biostatistics and Clinical disciplines.

Formal statistics for the HPA axis suppression studies were not described in the Biostatistics Review, and the small numbers of subjects tested for HPA axis suppression do not readily invite formal statistical analysis.

"From statistical point of view, the safety profile of Clobex Lotion is comparable to those Temovate E Cream (or Dermoval Cream for Study 2651) and Lotion vehicle in terms of the incidence of adverse events and cutaneous skin reaction."

The essential findings in the Biostatistics Review are the same as found in the Clinical Review, where they will be discussed (below) in the regulatory context of a 505(b)(2) submission.

E. Clinical Review dated (by Team Leader) 06/12/03:
The Medical Officer and Team Leader describe multiple conclusions:

1. "There is no doubt that clobetasol propionate as chemical moiety in a topical formulation is a super high potency anti-inflammatory drug product capable of treating corticosteroid responsive dermatoses. This was demonstrated in the two pivotal trials. Clobetasol propionate lotion (CP Lotion) was statistically superior to its lotion vehicle ($p \leq 0.001$)."
2. "In terms of efficacy, the Division allows for a 10% margin of non-inferiority compared to the RLD. In both the psoriasis trial and the atopic dermatitis trial, clobetasol propionate lotion had a margin of greater than 10% inferiority as compared to Temovate E (18.9% and 12.0%, respectively). In the atopic dermatitis trial, where the margin was closer to 10%, CP lotion failed in 3 of the 4 secondary variables, erythema, oozing/crusting, and pruritus."
3. "In terms of safety, while the cutaneous safety profiles of the two drug products are similar, the systemic safety profile, which in my opinion, is the major issue, of clobetasol propionate lotion is much worse than that of Temovate E Emollient Cream. The endpoint examined for systemic safety was the potential to suppress the HPA axis. CP Lotion

— However, this drug caused HPA axis suppression at some point during treatment of psoriasis in 80% of patients as compared to 33% in patients treated with Temovate E. Furthermore, at the end of the study 40% of patients had HPA axis suppression compared to 0% treated with Temovate E. This study further demonstrates that the potential for HPA axis suppression by clobetasol propionate lotion may be underestimated as the adrenal glands of the patients were constantly being stimulated (almost q week during the study) and suppression still occurred at the endpoint (4 weeks) for patients on CP Lotion but not in patients on Temovate E. Lastly, although the BSA treated in this study was higher than that approved for Temovate E, one has to assume that the comparison of the proportion of suppression between the two drugs, although lower, would be the same."
4. "The greater ability of CP lotion to cause HPA axis suppression is substantiated in the atopic dermatitis studies, of which the adolescent study is demonstrative. In this study 64.3% of patients experienced HPA axis suppression on CP lotion compared to 20% of those who used Temovate E."
5. "The time to recovery from HPA axis suppression was not clear for all the patients who had follow-up. A greater number did not recover in the time tested who were treated with clobetasol propionate lotion as compared to Temovate E Emollient Cream."
6. "The question to be answered ultimately in review of this application, when considering the risk/benefit analysis of clobetasol propionate lotion, is, ' Does clobetasol propionate lotion offer any advantage in the interest of the public health over the clobetasol propionate formulation that is currently marketed?' In my opinion, the answer is, 'No, it does not offer any advantage.' It is not efficacious as Temovate E Emollient Cream in treating corticosteroid responsive dermatoses while at the same time presents an

increased risk to the safety of the public health by having a poorer systemic safety profile as compared to Temovate E Emollient Cream."

The Medical Officer and Team Leader recommend "that the action taken for the new drug application of clobetasol propionate lotion be that of non-approvable."

I agree with some of their conclusions and not with others:

1. I agree that Clobex Lotion is superior to its lotion vehicle in effectiveness.
2. I agree that there was insufficient evidence to conclude that Clobex Lotion is non-inferior to the reference listed drug product, Temovate E Emollient Cream; however, I disagree that this would be an essential requirement for approval (see below).
3. I agree that the local safety profile is similar for Clobex Lotion and Temovate E Emollient Cream.
4. I disagree that the systemic safety profile of Clobex Lotion (which is regarded as " the major issue" in the Clinical Review) is "much worse than that of Temovate E Emollient Cream" (see below).
5. I agree that 9 of 14 adolescent patients with atopic dermatitis had evidence of HPA axis suppression associated with Clobex Lotion. This product will be indicated for adults only.
6. I disagree that "the question to be answered ultimately in review of this application, when considering the risk/benefit analysis of clobestasol propionate lotion, is, 'Does clobetasol propionate lotion offer any advantage in the interest of the public health over the clobetasol propionate formulation that is currently marketed'?" Pages 27-29 of Reinventing Drug & Medical Device Regulations, National Performance Review (April 1995) address the " Effectiveness of Drugs and Devices." The key passage states: " For the majority of new drugs and Class III devices, i.e., new products intended to treat less serious illness or provide relief from symptoms, a showing of effectiveness is usually based on a clinical trial comparing the product to a placebo. Such a showing does not involve a comparison to any other product."

I will address the remaining disagreements, which are 1) whether there is a requirement for demonstrating non-inferiority (in efficacy) to the reference listed drug product and 2) whether the systemic safety (HPA axis suppression) profile of Clobex Lotion is "much worse" than that of the reference listed drug product in the following analysis of this NDA.

The essential feature of a 505 (b)(2) application is that the applicant may rely on the Agency's finding of efficacy and/or safety from the labeling of a reference listed drug product by sufficiently comparing the bioavailabilities of their test product with the reference listed drug product. For topical products, bioavailability comparisons are generally obtained from clinical trials employing the endpoints of efficacy and safety. For topical corticosteroids there is generally also a comparative HPA axis suppression test (or tests, in the case of different dosing regimens in the same application).

The analysis of a 505 (b)(2) approach begins with the determination of the informational needs for a 505(b)(1) application according to current standards. Often, the reference listed drug product does not have labeling information sufficient for current standards, and the applicant must supply such additional information through studies they have conducted or obtained by right of reference. Also, the applicant may provide adequate information demonstrating efficacy or some aspect of safety that meets the needs for a 505(b)(1) application, such that they need not rely on the Agency's finding

from the labeling of the reference listed product for that particular informational need. Thus, the comparison of bioavailabilities with the reference listed drug product needs only to support the Agency's finding from the labeling of a reference listed drug product of that specific, essential information piece not otherwise provided by the applicant's studies or through right of reference.

Often, topical product NDAs are 505 (b)(2) applications in which the sponsor relies on the Agency's finding of efficacy from the labeling of a reference listed drug product, e.g., when the vehicle is sufficiently different from that of the reference listed drug product owned by a different manufacturer. In such cases, the sponsor must demonstrate non-inferiority to the reference listed drug product and superiority to the new vehicle. Although this has been a common architectural feature of the information structure in many 505 (b)(2) applications, the finding of non-inferiority to the reference listed drug product is not essential, if the applicant provides sufficient information separately to document effectiveness. The comparative bioavailability bridge need only support the Agency's finding from the labeling of the reference listed drug product for which the applicant has not otherwise produced sufficient evidence through studies they have conducted or through right of reference.

This NDA adduces sufficient evidence for efficacy for a 505 (b)(1) application, viz., two adequate and well-controlled studies (9707 and 18001) in which the product is clearly superior to vehicle. Accordingly, there is no need to demonstrate non-inferiority to the referenced listed drug product, since the applicant is not relying on the Agency's finding of efficacy from the labeling of the reference listed drug product. The demonstration of superiority to vehicle in psoriasis and atopic dermatitis in separate studies is sufficient for the corticosteroid – responsive dermatoses indication.

In addition to evidence for efficacy, the analysis of a 505 (b)(2) approach involves the determination of the informational needs for safety for a 505(b)(1) application according to current standards. Evidence for safety is divided into two parts: non-clinical and clinical. The first part, non-clinical, has not been established independently by the applicant in this NDA, and the applicant is relying on the Agency's finding of non-clinical safety from the labeling of the reference listed drug product. Also, the applicant has made specific post-marketing commitments to provide additional non-clinical safety information for informational needs that could be provided post-approval for the same product in a strictly 505 (b)(1) application.

The clinical evidence for safety in this NDA is divided into two parts: local and systemic. Both the Clinical Review and the Biostatistics Review conclude that Clobex Lotion and Temovate E Emollient Cream have similar local safety findings. Both the Clinical Review and the Biostatistics Review conclude that Clobex Lotion was not found to be non-inferior to Temovate E Emollient Cream according to the efficacy endpoints. Accordingly, the logic of 320.24 (b)(4) would indicate that the rate and extent of absorption of the active ingredient in Clobex Lotion at the site of action, viz., locally, would be at most equivalent to, and plausibly somewhat less than, Temovate E Emollient Cream. If Clobex Lotion is at most equivalent to Temovate E Emollient Cream, then it is permissible to rely on the Agency's findings of local safety for the active moiety from the labeling of the reference listed drug product. The additional evidence for local safety from studies 9707, 2651, and 18001 and from the requisite human dermal safety studies,

2129 and 1802, is sufficient to conclude that the local safety information base is adequate and that local safety is acceptable for the intended use of the product.

The clinical evidence for systemic safety for topical (gluco-) corticosteroids is generally derived from HPA axis suppression studies. There are general aspects of such HPA axis suppression studies and utility of outcomes that are independent of this specific NDA that must be considered before addressing the evidence in this NDA. Importantly, the primary clinical utility of HPA axis suppression study outcomes is whether HPA axis may occur at maximal duration, amount per week, and body surface area involved, according to labeled conditions of use. Very precise point estimates of HPA axis suppression "risk" provide minimal additional utility, since there are many variables that determine whether suppression occurs, such as prior corticosteroid use, body surface area of involvement, anatomic region of involved skin, thickness of product application, etc. It is not uncommon for HPA axis suppression studies to show suppression in patients with smaller body surface areas of involvement compared with patients with larger body surface areas of involvement who do not suppress. There is no adequate model based on these variables that can predict who will suppress. Accordingly, it is not possible to incorporate a very precise point estimate from HPA axis suppression studies of new drug products into a heuristic that will allow a clinician to determine which patient is at risk for suppression. At best, HPA axis suppression studies can identify risk at maximal conditions of labeled use as unlikely, possible, or probable.

Because of the multiple degrees of freedom in the topical corticosteroid-induced adrenal suppression model, the ability of comparative adrenal suppression studies to detect true differences in the potential for adrenal suppression between two products depends on the numbers of subjects tested and the degree to which the identifiable variables are controlled. In most comparative adrenal suppression studies the large number of identifiable variables and difficulty in recruiting such patients into the study preclude strong inferences regarding differences in potential for adrenal suppression between two products, especially when numbers of subjects actually tested are small.

This NDA includes studies of HPA axis suppression comparing Clobex Lotion and Temovate E Emollient Cream for both four weeks' duration in adult patients with psoriasis (Study 9708) and two weeks' duration in adult patients with atopic dermatitis (Study 18009). In Study 9708, 8 of 10 patients suppressed with Clobex Lotion and 3 of 10 patients suppressed with Temovate E Emollient Cream. The requisite condition for the Chi-Square Test, a minimum of 5 per cell, is not met, since half of the cells have counts less than 5. Two-sided Fisher's Exact Test computationally gives $p \leq 0.07$; however, for this test the assumption of fixed margins is very restrictive for interpretation of findings. Simply stated, the denominators are too small to provide strong inferences by statistical methods. In Study 18009, 5 of 9 patients suppressed with Clobetasol Lotion and 4 of 9 patients suppressed with Temovate E Emollient Cream. Two-sided Fisher's Exact Test computationally gives a probability of 1.00; however, for this test the assumption of fixed margins is very restrictive for interpretation of findings. The denominators are even smaller than Study 18009. Thus, in adult patients with psoriasis and atopic dermatitis, Clobex Lotion demonstrated rates of HPA axis suppression that were numerically higher than those of Temovate E Emollient Cream, although the small numbers studied do not allow for strong statistical inferences that Clobex Lotion is

"much worse" than Temovate E Emollient Cream in the potential for causing HPA axis suppression.

However, it is fair to state that both Clobex Lotion and Temovate E Emollient Cream present a relatively high risk for HPA axis suppression when used at maximal conditions of labeled use. There are clear statements of such risk in the final draft labeling agreed to by the sponsor, along with limiting the indication to adults only and stating explicitly that "use in patients younger than 18 years of age is not recommended due to numerically high rates of HPA axis suppression."

In sum, I find that adequate evidence has been provided in this NDA to find that this product is safe and effective for its intended use per labeled conditions, including precautionary language regarding the potential for HPA axis suppression. A post-marketing commitment to conduct HPA axis suppression tests without interim adrenal stimulation will provide useful information for product labeling in the future

F. Conclusion

This NDA is sufficient for approval since the sponsor has committed to perform the recommended post-marketing studies, both non-clinical and clinical, and has accepted the final draft labeling proposed to sponsor.

/S/

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
7/24/03 03:03:14 PM
MEDICAL OFFICER

EXHIBIT 33

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-535

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-535

Galderma Laboratories, L.P.
Attention: Paul M. Clark
Vice President, Regulatory Affairs
14501 N. Freeway
Fort Worth, TX 76177

Dear Mr. Clark:

Please refer to your new drug application (NDA) dated September 25, 2002, received September 27, 2002, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Clobex (clobetasol propionate) Lotion, 0.05%.

We acknowledge receipt of your submissions dated January 10, January 27, January 28, February 6, February 10, February 19 (2), February 27, April 24, May 9, June 10, July 1, July 3, July 7, and July 22, 2003 (facsimile).

This new drug application provides for the use of Clobex (clobetasol propionate) Lotion, 0.05%, for treatment of corticosteroid responsive dermatoses.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission **"FPL for approved NDA 21-535."** Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated July 22, 2003. These commitments are listed below.

1. The Applicant commits to performing dermal carcinogenicity testing of the drug product.

   Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter
Study Start: Within 6 months of the date of the approval of the protocol
Final Report Submission: Within 12 months after the study completion

2. The Applicant commits to a study to evaluate the effects of the drug product on UV-induced skin cancers.

   Commitment Category: NON-CLINICAL TOXICOLOGY

   Protocol Submission: Within 4 months of the date of this letter
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 12 months after the study completion

3. The Sponsor commits to performing an HPA axis suppression study in no less than 60 evaluable patients using cosyntropin stimulation testing (conducted as labeled with stimulated serum cortisol levels at 30 minutes with any suppressed patients followed to recovery, stimulation should only be conducted at baseline and at the end of the two or four week treatment period) in adult patients with psoriasis or atopic dermatitis. Clobex Lotion should be applied to lesional skin at the maximum amounts permitted in labeling.

   The minimum number of subjects (separate cohorts for each) committed to are as follows:
   a) no less than 30 evaluable adult patients with psoriasis or atopic dermatitis of no less than 20% BSA after 2 weeks of treatment
   b) no less than 30 evaluable adult patients with psoriasis of no less than 10% BSA after 4 weeks of treatment

   Commitment Category: CLINICAL SAFETY ASSESSMENT
   Protocol Submission: Within 4 months of the date of this letter
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 16 months after approval of the protocol

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Melinda Harris, M.S., Regulatory Project Manager, at 301-827-2020.

Sincerely,

{See appended electronic signature page}
Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation & Research

Enclosure (Labeling)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
7/24/03 03:15:00 PM